REMARKS/ARGUMENTS

Claims 17, 20-24, 26-28, 30 have been amended. Claims 33-42 have been added. Claims 18-19, 25, 29, and 32 have been cancelled. These amendments are made for better format of the claims. Support for the amendments can be found at, e.g., originally filed claims 1-16, previously filed claims 17-27, paragraph nos. 0017-0067 and Examples 3-4 of the published specification. No new matter is added. Entry of the amendments is respectfully requested. Upon entry of the amendments, claims 17, 20-24, 26-28, 30-31 and 33-42 are pending. Reconsideration of the present application is respectfully requested in view of the above amendments and the following remarks.

Claims 28, 30, and 31 are withdrawn from consideration due to the unity requirement under the pertinent PCT rule. Note that for reasons expressed below, claim 17 is patentable in view of the prior art. Therefore, claims 28, 30, 31 and their dependent claims, which all refer to claim 17, share the same inventive concept as claim 17 and meet the unity requirement under the relevant PCT rule. Consideration of claims 28, 30, 31, and their dependent claims, is respectfully requested.

Claim Objection

Claim 25 is objected to due to several informalities, which have now been corrected as suggested by the Examiner. Withdrawal of the objection is therefore respectfully requested.

Claim Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 17-27 are rejected under 35 U.S.C. § 112, second paragraph due to several informalities. These informalities have now been obviated in the currently presented claims. Note that in response to the Examiner's objection to the term "effective and non-excessive amount" recited in claim 17 as being indefinite, Applicant has now further clarified the meaning of this term by referring to the desired cross-linking degree in claim 17. Therefore, Applicant

respectfully requests that the rejections of claims17-27 under 35 U.S.C. § 112, second paragraph be withdrawn.

Claim Rejections under 35 U.S.C. § 102

Claims 17, 26, and 27 are rejected under 35 U.S.C. § 102(b) as being anticipated by Kuniak et al. (CA949965).

Kuniak discloses starch grains (granules having an "organized" native structure within which amylose and amylopectin co-exist and bound together). Nowhere does Kunicak disclose cross-linking a mixture of at least two different hyaluronic acid salts as recited in claim 17. Therefore, claim 17 is not anticipated by Kuniak under 35 U.S.C. § 102(b). For at least the same reasons, Kuniak does not anticipate claim 26 or claim 27, each of which depends from claim 17.

Claims 17-20, 26, and 27 are rejected as anticipated by Balazs et al. (US 4582865), which may be further evidenced by Desia et al. (J. Pharm Sci. 1995 Feb; 84(2):212-5, abstract). According to the Examiner, Balazs teaches the cross-linking of sodium hyaluronate, or sodium hyaluronate with other polymers, such as collagen and heparin. The Examiner relies on Desia to show that it is well known in the art that hyaluronans in one product have molecular weight dispersity, and other polymers such as collagen and heparin have different molecular weights from hyaluronans. But Balazs teaches nowhere the cross-linking a mixture of at least two different hyaluronic acid salts as recited in claim 17.

Note that as is apparent from the specification of the present application (*see* e.g., paragraph nos. 0021-0031 and Examples 3-4 of the published specification), two different hyaluronic acid salts refers to two preexisting products, which are different from only one preexisting product which may have some molecular dispersity, as argued by the Examiner. This is also consistent with the prior art well-known understanding. For example, as shown at F.H. Silver *et al.* in the Journal of Applied Biomaterials, Vol. 5, 89-98 (1994) (copy attached as Exhibit 1),

page 90, second full paragraph, and page 93, Table II, a high molecular weight of polymer (such as HPMC and HA) is a different product than a low molecular weight of the same polymer. Indeed, due to a different degrees of polymerization, which leads to a different molecular weight and viscosity, one type of polymer, such as HPMC, may have many different pre-existing products.

See, e.g., http://www.ginshicel.cn/MHPC.html. Copy of this web page is attached as Exhibit 2.

Therefore, Balazs, as evidenced by Desia, also fails to anticipate claim 17 and any of its dependent claims 18-20, 26, and 27 under 35 U.S.C. § 102(b).

Claims 17-20 and 26-27 are rejected under 35 U.S.C. §102(b) as anticipated by Malson et al. (US 4716154).

Malson discloses a gel of cross-linked hyaluronic acid for ophthalmological uses. But nowhere does Malson teach, disclose, or suggest cross-linking a mixture of at least two different hyaluronic acid salts as recited in claim 17 of the present application. The Examiner again states that due to the molecular weight dispersity in one polymer product, the hyaluronic acid salt used in Malson is "extremely likely" to contain HA of molecular weight less than 990,000Da and HA with a molecular weight of more than 1,000,000Da. As explained above in detail, one HA product with molecular weight dispersity is not the same as or similar to two different pre-existing HA products. Therefore, Malson cannot anticipate claim 17 or any of its dependent claims 18-20 and 26-27 under 35 U.S.C. §102(b).

Withdrawal of the rejections under 35 U.S.C. § 102(b) is therefore respectfully requested.

Claim Rejections under 35 U.S.C. § 102(b) and/or 103

Claims 21-25 are rejected as anticipated by or, in the alternative, obvious over Malson, *supra* under 35 U.S.C. §102(b) and/or 35 U.S.C. §103(a).

As discussed above, nowhere does Malson teach, disclose, or suggest cross-linking a mixture of at least two different hyaluronic acid salts as recited in claim 17 of the present

application. Therefore, Malson cannot anticipate or render obvious claims 21-25, which all depend from claim 17.

The Examiner also cites to *KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. 398, 82 USPQ2d 1385 (2007) and states that it would have been obvious for a person of ordinary skill in the art to arrive at the present invention by arranging old elements (cross-linking HA of different molecular weights), which all perform the same function they had been known to perform (gel formation). Applicant disagrees.

First, the Examiner does not clearly articulate a valid reason to support the legal conclusion of obviousness, as required by *KSR*. As noted above, Malson discloses a gel of only one cross-linked hyaluronic acid product for ophthalmological uses. Without any valid reason, a person of ordinary skill in the art would not complicate a process by using two different HAs as suggested by the Examiner.

Also, as cited by the Examiner, KSR states that "[t]he combination of familiar elements according to known methods is likely to be obvious **when it does no more than yield predictable results**." (Emphasis added.) Here, the inventor of the present application surprisingly found that cross-linking two different types of polymers satisfies the following specifications for an injectable hydrogel product: (1) monophase; (2) better mechanical properties and remanence than the equivalent products of the prior art; (3) unaffected or even improved injectability that is still possible with conventional injection forces using conventional injection devices. *See*, for examples, paragraph nos. 0021-0031 of the published specification. None of these results would have been predictable to a person of ordinary skill in the art based on the teachings of Malson, which does not even mention anything about an injectable hydrogel product.

Therefore, based on *KSR*, none of the claims of the present application is obvious in view of Malson under 35 U.S.C. § 103(a). Withdrawal of the rejections of claims 21-25 in view of Malson under 35 U.S.C. §102(b) and/or 35 U.S.C. §103(a) is respectfully requested.

Based on the foregoing, the present application has been placed in condition of allowance. Early and favorable consideration is respectfully requested.

It is believed that no fees or charges are required at this time in connection with the present application. However, if any fees or charges are required at this time, they may be charged to our Patent and Trademark Office Deposit Account No. 03-2412.

Respectfully submitted,
COHEN PONTANI LIEBERMAN & PAVANE LLP

By _____

Edward M. Weisz
Reg. No. 37,257
551 Fifth Avenue, Suite 1210
New York, New York 10176
(212) 687-2770

Dated: January 29, 2009

Physical Properties of Hyaluronic Acid and Hydroxypropylmethylcellulose in Solution: Evaluation of Coating Ability

Frederick H. Silver,* Joseph LiBrizzi,* George Pins,* Ming-Che Wang,* and Dominick Benedetto†

*Department of Pathology, University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School, Piscataway, New Jersey and †Cataract and Primary Eye Care Service, Wills Eye Hospital, Philadelphia, Pennsylvania

Hyaluronic acid (HA) and hydroxypropylmethylcellulose (HPMC) in buffered saline are "viscoelastics" used in ophthalmic surgery to prevent mechanical damage to delicate eye structures and to form a protective coating over corneal endothelium.

HA is a high molecular weight polysaccharide that exhibits decreasing viscosity at increased shear rates. HPMC is a cellulose derivative that exhibits low surface tension. This study examines the physical properties of HA and HPMC solutions and attempts to correlate these properties with the ability of those macromolecules to coat and protect ocular structures.

Results presented in this article suggest mixtures of HA and HPMC exhibit low surface tension and ease of aspiration characteristics that are desired in viscoelastic materials. For this reason a blend of these two macromolecules offers handling advantages over each of these individual macromolecules. © 1994 John Wiley & Sons, Inc.

INTRODUCTION

Solutions of flexible macromolecules are routinely used in ophthalmic surgery. Generically referred to as viscoelastics, these solutions are used to reinflate the eye after the initial surgical wound releases intraocular aqueous or vitreous humor. Because these solutions possess high viscosity at rest, the eye remains inflated and intraocular tissues resume their normal relationships during intraocular surgical manipulations. Viscoelastic solutions protect intraocular tissues during surgery especially the corneal endothelium and facilitate the insertion and exit of intraocular lens prosthetics and surgical instruments.[1-3]

Polymeric materials used in formulating these solutions include hydroxypropylmethylcellulose (HPMC), hyaluronic acid (HA), chondroitin sulfate (CS), polyacrylamide, collagen, and mixtures of some of these materials. All of these molecules except collagen and polyacrylamide are polysaccharide derivatives and exhibit the conformational freedom that allows these molecules to exhibit flexibility in solution.[1] This produces the desired clinical handling properties. Collagen is a triple helical protein that exhibits a high chain stiffness at neutral pH.

Solutions presently in use can be placed in three general categories based on clinical properties: solutions of HA (Healon™ and AMVISC), a solution of HPMC (Occucoat™), and a heterogenous solution containing HA and CS (Viscoat™).

Solutions of HA alone possess a very high viscosity at rest, shear thin during injection, aspirate as a bolus because of high solution cohesion, and possess relatively high surface tension. The solution of HPMC is less viscous at rest, does not shear thin as well as solutions of HA, is less cohesive, retards aspiration, and has lower surface activity than HA. The heterogenous solution of HA and CS has properties of both solutions of HA and HPMC. Surgeon preferences and specific tasks determine viscoelastic selection. Postsurgical intraocular pressure and loss of endothelial cells is dependent on the viscoelastic used.[3-5]

HA is a polymer of the monosaccharides β-D-glucuronic acid and β-D-*N*-acetyl-galactosamine in the $^4C_1$ or C1 chair conformation.[6] Theoretical free energy calculations indicate that the C1 chair conformation of glucose derivatives is more stable than the boat conformation, and that combinations of β (1–3) or (1–4) linkages as found in HA appear to center around the extended conformation of (0°, 0°) with a rotational flexibility of about 50°.[6] These data suggest that the HA molecule has inherent flexibility because of the mix of β (1–3) and β (1–4) linkages.[7]

Although HA molecules are inherently flexible, hydrogen bond formation theoretically stiffens the chain backbone[8] under low-shear conditions and, under high-shear states, breakage of these bonds would lead to shear thinning. However, shear thinning may also involve breakage of bonds between different molecules that form a network structure recently described.[9] Yanachi and Yamaguchi[10] reported that HA solutions with viscosity-averge molecular weight of less than 35×10^4 are

Requests for reprints should be sent to Frederick H. Silver, Ph.D., Biomaterials UMDNJ–Robert Wood Johnson Medical School, 675 Hoes Lane, Piscataway, NJ 08854

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CCC 1045-4861/94/010089-10

molecularly dispersed in solution and, in comparison, solutions containing molecules with viscosity-average molecular weight, 160 × 10^4 or above, exhibited a saturated network structure.

HPMC is a derivative of cellulose, a polysaccharide found in wood and other natural structures. Cellulose is a polymer of β-D-glucose with (1–4) linkages and forms an extended structure based on X-ray diffraction data.[11] The chains are extended in ribbon-like conformations, with two sugar rings repeating every 1.03 nm. Treatment of cellulose with alcohols or ketones results in derivatives that have reduced hydrogen bonding potential. Replacement of hydroxyl by methoxy groups is achieved up to 29% of the time and by hydroxypropyl groups up to 8.5% of the time in a typical raw material.[3]

Below we examine the physical properties of HA and HPMC solutions and attempt to correlate these properties with the clinical performance of these macromolecules.

MATERIALS AND METHODS

HA and HPMC

Hyaluronic acid was obtained from Genzyme Corporation (Cambridge, MA) lot numbers C 1380B, C0191, C 9340, C0193 with reported analyses as listed in Table I. Molecular weights reported for lots C0191 and C 1380 B average 0.8 × 10^6 and those for lots C0193 and C 9340 average 2.1 × 10^6. Lots C0191 and C 1380 B are subsequently referred to as low molecular weight and the other two lots as high molecular weight (C0193 and C 9340). HA was used as received.

HPMC was obtained form Sigma Chemical Co. (St. Louis, MO) H-7509 lot 117F0582 and H-8384 lot 29F0349. The viscosities (2% solutions) of the respective lots were 4000 cps and 50 cps, respectively. HPMC was used as received without further purification. Low and high viscosity HPMCs will be referred to as low and high molecular weight HPMC, respectively.

Solution Preparation

HA and HPMC were dissolved in neutral salt buffers containing 0.85% (w/v) sodium chloride, 0.028% (w/v) disodium hydrogen phosphate, and 0.004% (w/v) sodium dihydrogen phosphate hydrate dissolved in distilled water at pH 7.2. Solutions were serially diluted using the neutral salt solution to obtain dilution factors of up to 1 000 000 X.

Surface Tension and Contact Angle

Surface tension was measured at 25 °C using a tensiometer (Cahn, Model DCA-322, Cerritos, CA). Twenty milliliters of each solution was prepared by dissolving the polymer in the neutral salt buffer described above at concentrations ranging from 1 mg/mL (10X) to 0.01 μg/mL (10^6X). Solutions were poured out into a Pyrex cover dish and placed on the stage of the tensiometer. A glide cover glass was flamed and mounted in the stirrup of the tensiometer and data collected at room temperature using a platform speed of 104 μ/s. Calibration of the tensiometer was performed by placing weights on the stirrup counterbalance to offset the glass slide weight until a reading between 0 and 70 mg was produced. Data was collected and analyzed using an IBM-PC and DCA-322 software to obtain surface tension of the receding curve for each material tested.

Viscosity Measurements

Solutions were removed from storage at 4 °C and allowed to reach room temperature. After reaching room temperature, 5 mL of each solution was injected into the cup of a Haake CV 100 Rotoviscometer (Haake, Inc., Paramus, NJ) fitted with a ZA 30 sensoring system. The shear rate was linearly increased from 0.3 to 9.0 s^{-1} over a period of 9 min and the viscosity of the solution recorded with a Haake RV 100 plotter. From a plot of viscosity versus shear rate, the viscosity at 0.35 s^{-1} was extrapolated.

Light Scattering

Weight average molecular weights were determined from the scattered light intensity at an angle of 6 to 7° using a Chromatix KMX-6 laser light scattering device as previously described.[12] The optical constant required for molecular weight determinations was obtained using a

Table I. Reported Analyses of Genzyme Hyaluronic Acid

Lot Number (Date)	Absorbance at 257 nm	Protein (%)	Chlorine (%)	pH (1% Solution)	Purity (%)	Molecular Weight
C0193 (7/17/91)	0.0	BDL	2.9%	6.1	100	2.1 × 10^6
C9340 (11/9/89)	0.0	BDL	BDL	6.2	100	2.1 × 10^6
C0191 (6/11/90)	0.0	BDL	BDL	5.7	100	0.9 × 10^6
C1380 B (11/12/91)	0.0	BDL	0.1%	5.8	100	0.7 × 10^6

All molecular weights determined by viscometry. BDL, background detectable level.

Chromatix KMX-16 differential refractometer operating at 5 °C and at a wavelength of 633 nm. The instrument was calibrated by measuring the difference in refractive index of standard salt solutions with water as the reference material. Once the calibration constant was determined from measurements on salt solutions, the difference in refractive index between each solution and its dialysate was measured at concentrations between 1 and 5 mg/mL. The ratio of the change in refractive index, Δn, divided by the concentration, c, was plotted against concentration, and the value of the refractive index was taken as $\Delta n/c$ extrapolated to zero concentration.

Molecular weight was then obtained by determining the excess Rayleigh factor (R_θ) for solutions of known concentration, c, between 0.1 and 0.5 mg/mL and plotting KC/R_θ against concentration (K the optical constant is calculated using refractive index increment) as shown in Figure 1. Weight average molecular weight was determined from the reciprocal of KC/R_θ extrapolated to zero concentration.

Injection Tests

Injection load versus time curves (see Fig. 2) were constructed for solutions of HA and HPMC using specially designed syringe holders built to attach to the compression cell of an Instron Model 1122. Force was measured from the load cell and the crosshead was lowered at a rate of 200 mm/min. Maximum stress was determined by dividing the peak load by the cross-sectional area of the syringe.

Aspiration Behavior

The ability of HA and HPMC solutions to be aspirated through a 23-gauge needle was determined by placing a vacuum on each sample and determining the fraction of sample aspirated within 1 min. The vacuum was increased in 20 mmHg increments from 0 to 100 mmHg and the fraction aspirated was determined gravimetrically.

Statistics

All values are reported as mean ±SD and compared statistically using a one-tailed, unpaired Student's t-test. Each point shown is the mean of at least three measurements. A p value of less than 0.05 was used to determine significant differences.

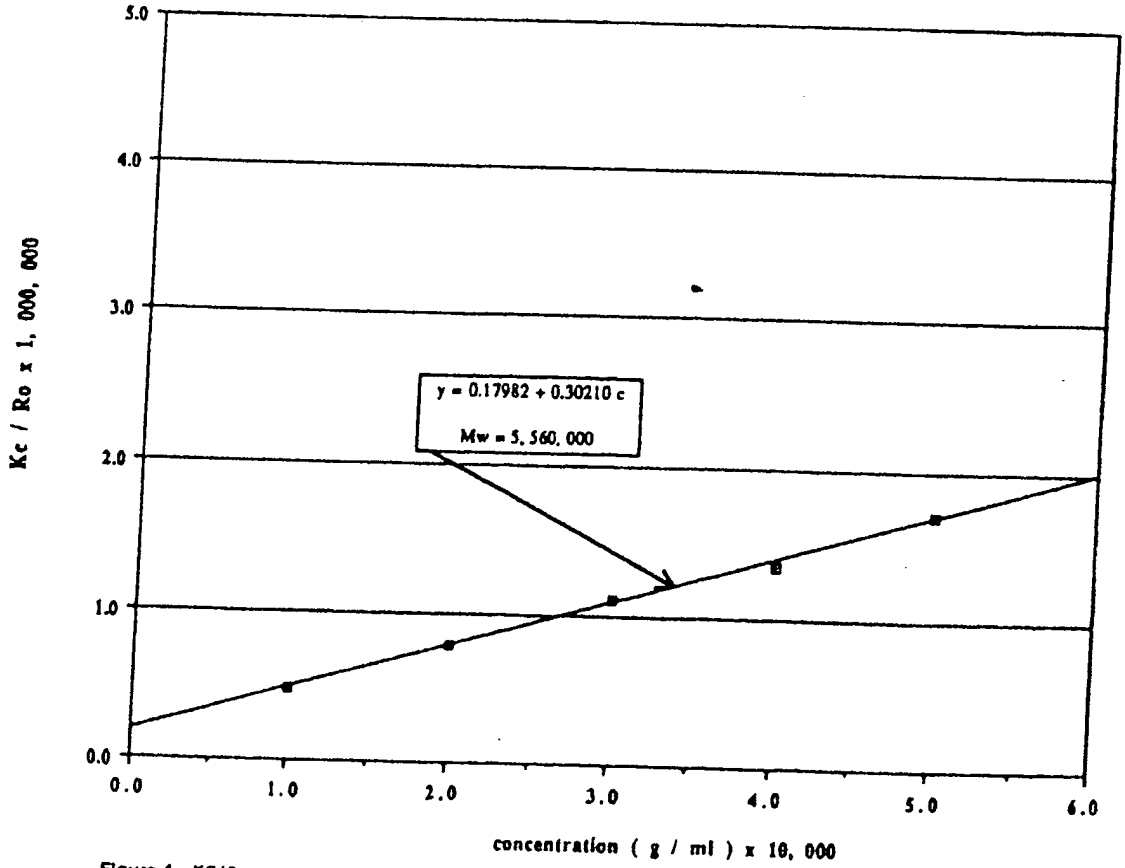


Figure 1. KC/R_θ versus concentration, C, for high molecular weight HA. The molecular weight was obtained from the inverse of the abscissa extrapolated to zero concentration. The calculated molecular weight was 5 560 000.

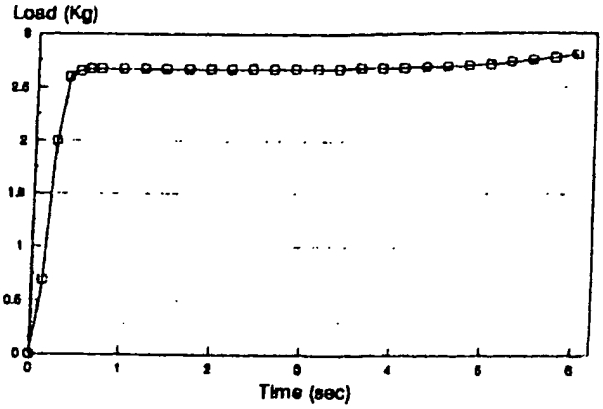


Figure 2. Typical maximum load versus time for high molecular weight HA. The maximum load was determined as the largest load needed to force a sample of viscoelastic from a syringe through a 23-gauge needle.

RESULTS

Surface Tension Measurements

Figure 3 shows a typical surface tension versus dilution curve for HA. As shown in Figure 4 the surface tension for Occucoat at a 1:10 dilution was found to be 43.0 ± 1.41 dynes/cm and that for Healon was 62.7 ± 6.51 dynes/cm, significantly higher ($p \geq 0.05$). Values for pure HPMC, both low molecular weight (L) and high molecular weight (H) solutions were about 50 ± 0.75 and those for pure HA, both H and L were above 70 ± 2.25 dynes/cm. Mixtures of 1% HA and 2% HPMC had surface tensions that were about 50 ± 0.58 dynes/cm, similar to solutions of pure HMPC.

Weight Average Molecular Weight

A typical plot of KC/R_θ versus concentration used to calculate weight molecular weight based on light scattering is shown in Figure 1. Values of molecular weigh for HA obtained were 807 000 (L) and 5 560 000 (H Mixtures of HA and HPMC had molecular weights 435 000 [HA (L) + HPMC (L)], 5 370 000 [HA (H and HPMC (L)], 568 000 [HA (L) and HPMC (H)], an 5 370 000 [HA (H) and HPMC (H)]. Experimental value of the weight average molecular weight are tabulated i Table II.

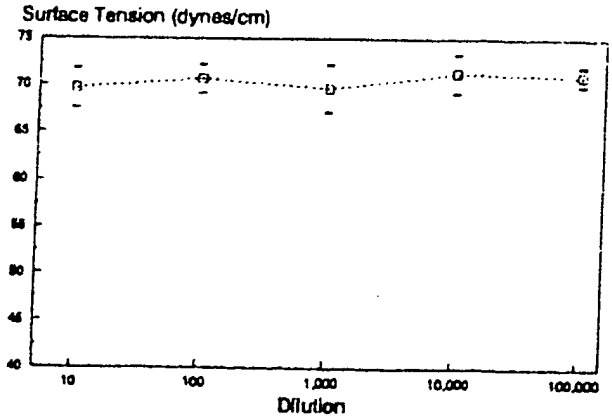


Figure 3. Typical plot of surface tension versus dilution for high molecular weight HA at 25 °C. The measured surface tension was 70 ± 2.25 dynes/cm². No significant difference was observed between the surface tension at different dilutions.

Low Shear Viscosity

A typical plot of viscosity versus shear rate is shown in Figure 5. Figure 6 shows a comparison between the viscosities at a shear rate of 0.35^{-1} of HA, HPMC, and mixtures of HA and HPMC solutions. The viscosity of Healon™ and Occucoat™ were found to be 25 000 and 4000 mPas, respectively. The viscosity of 2% HPMC solutions are 98 (L) and 3680 mPas (H) and 1% HA are 424 (L) and 21 845 mPa · s (H). Mixtures of 1% HA and 2% HPMC have viscosities of 2095 mPa · s [HPMC (L) and HA (L)], 38 460 mPa · s [HPMC (L) and HA (H)], 24 344 mPa · s [HPMC (H) and HA (L)], and 56 691 mPa · s [HPMC (H) and HA (H)]. Although HPMC solutions have low viscosities alone, when they are added to HA solutions an increased viscosity is noted.

Aspiration Behavior of HA and HPMC

Typical aspiration plots for HA, HPMC, and mixtures are shown in Figures 7–10. The aspiration behavior of HA is approximately sigmoidal. At low vacuum only small amounts of HA can be aspirated but at vacuums of about 40 mmHg almost 100% of the HA sample can be removed. In contrast, the amount of HPMC removed is almost linear with a pressure increase until it is all removed. As the molecular weight of HPMC is increased the amount of the sample removed by aspiration at a fixed pressure is decreased.

Mixtures of HA and HPMC containing low molecular weight HPMC aspirate in a similar fashion to pure HPMC solutions. Solutions of high molecular weight HPMC are more difficult to aspirate compared with pure solutions of either HA or HPMC.

Injection Curves

A typical load versus time plot is shown for HPMC and HA solutions through a 3-cc syringe in Figure 2. Figure 11 shows a comparison of the maximum stresses required to inject solutions of HPMC and HA through syringes of different sizes; the maximum stress decreases as the diameter of the syringe decreases. Figure 12 shows that the viscoelastic flow rate proportional to strain rate is linearly dependent on the maximum stress on the syringe.

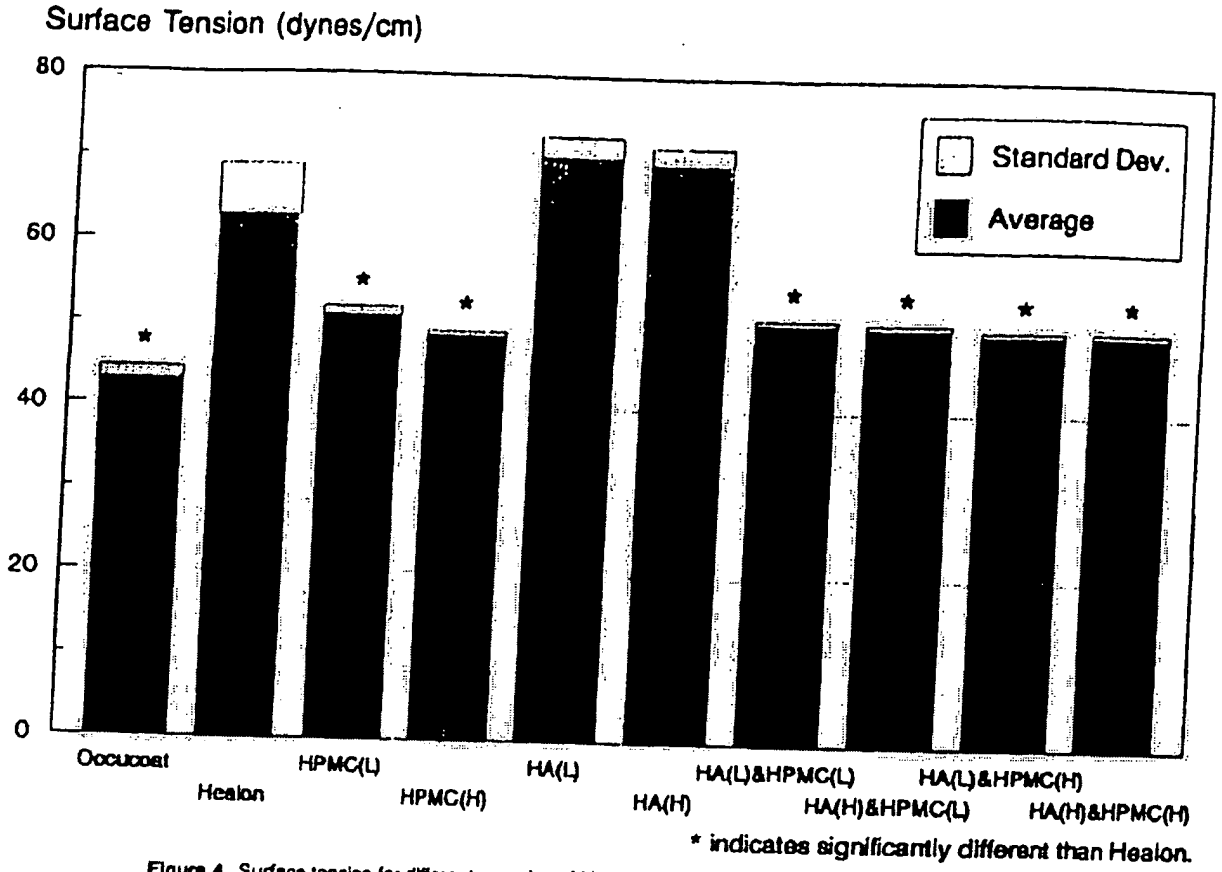


Figure 4. Surface tension for different samples of HA, HPMC, and combinations of HA and HPMC in neutral buffer at 25 °C and a dilution of 1:10. Surface tension for Healon, and low and high molecular weight HA was significantly higher than the value obtained for solutions containing 2% HPMC, and mixtures of 1% HA and 2% HPMC. HPMC (L), low molecular weight HPMC; HPMC (H), high molecular weight HPMC; HA (L), low molecular weight HA; HA (H), high molecular weight HA.

DISCUSSION

HA and HPMC are used clinically in buffered saline solutions to prevent mechanical damage to the corneal endothelial cells and to maintain the shape of the anterior chamber allowing surgical manipulation of instruments. Viscoelastics containing high molecular weight HA are reported to maintain the deepness of the anterior chamber better than HPMC,[13] and can be removed completely by aspiration. In contrast, HPMC solutions form an endothelial coating visible under the operating microscope and are more difficult than HA to aspirate from the anterior chamber.[13] Finally, elevation of the postoperative intraocular pressure has been reported after injection of HA solutions into the anterior chamber[4,5,14] and HPMC solutions did not cause postsurgical hypertension.[14,15] These data suggest that each of these macromolecules has physical properties that are advantageous in some aspect of ophthalmic surgery. The purpose of this research was to try to understand the molecular basis for the different macromolecular behaviors observed, compare the physical properties of HA and HPMC, and attempt to explain the different clinical behaviors of these materials.

Table II. Weight Average Molecular Weights of Viscoelastic Solutions Determined by Low-Angle Light Scattering

Solution	Weight Averaged Molecular Weights (r^2)
HA (L)	807 000 (0.895)
HA (H)	5 560 000 (0.994)
HPMC (L)	123 000 (0.846)
HPMC (H)	330 000 (0.904)
HA (L)/HPMC (L)	435 000 (0.978)
HA (H)/HPMC (L)	5 370 000 (0.998)
HA (L)/HPMC (H)	568 000 (0.996)
HA (H)/HPMC (H)	5 370 000 (0.996)

Coefficient of correlation (r^2); fraction of variation in KC/R_θ value that can be explained by linear extrapolation of light scattering data.

It has been suggested that the ability of HA solutions to maintain the deepness of the anterior chamber reflects the elasticity of this material.[13] From classical studies on syn-

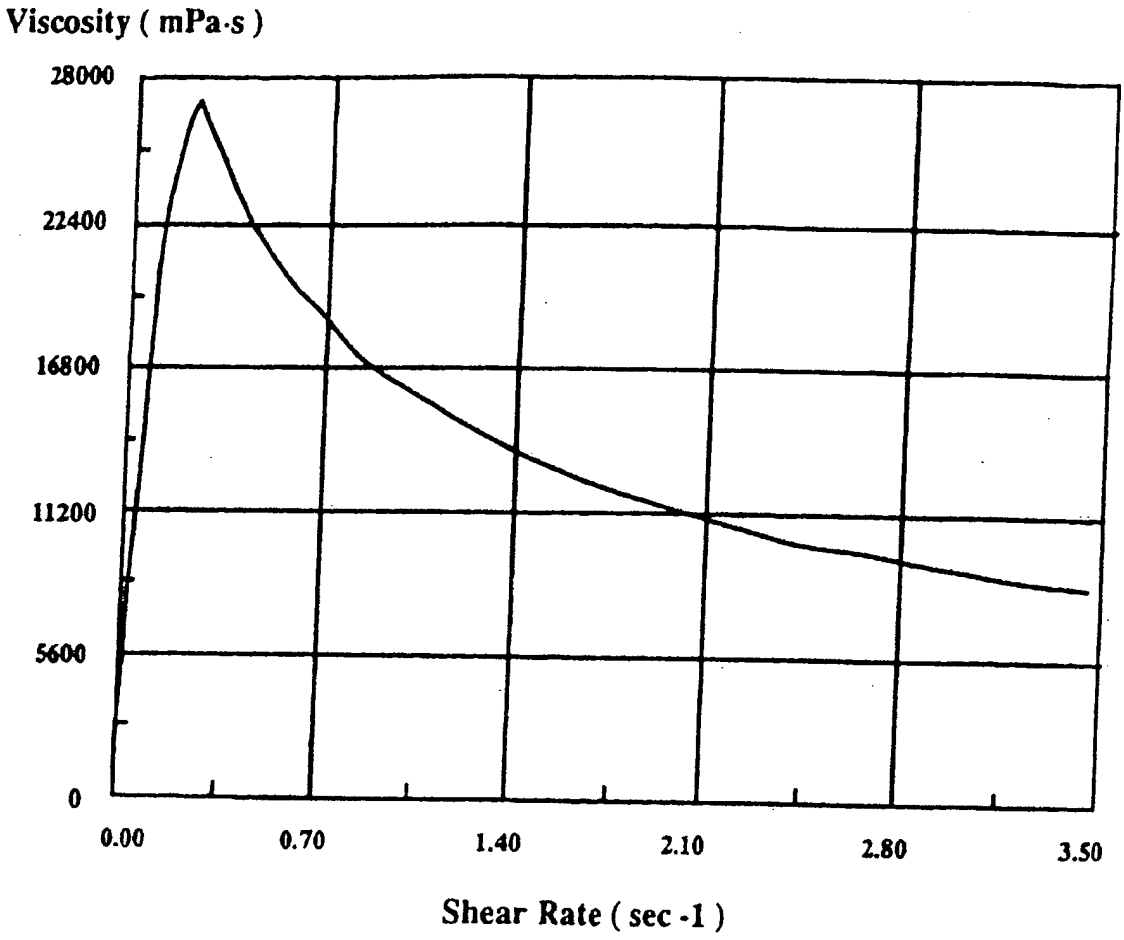


Figure 5. Typical viscosity versus shear rate for high molecular weight HA. Data used in Figure 6 was obtained at a shear rate of 0.35 s^{-1}.

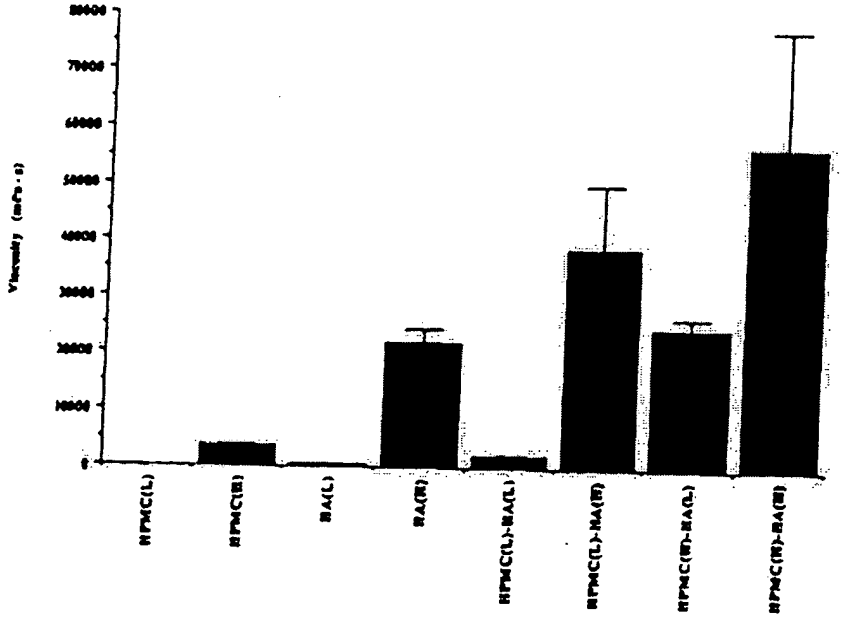
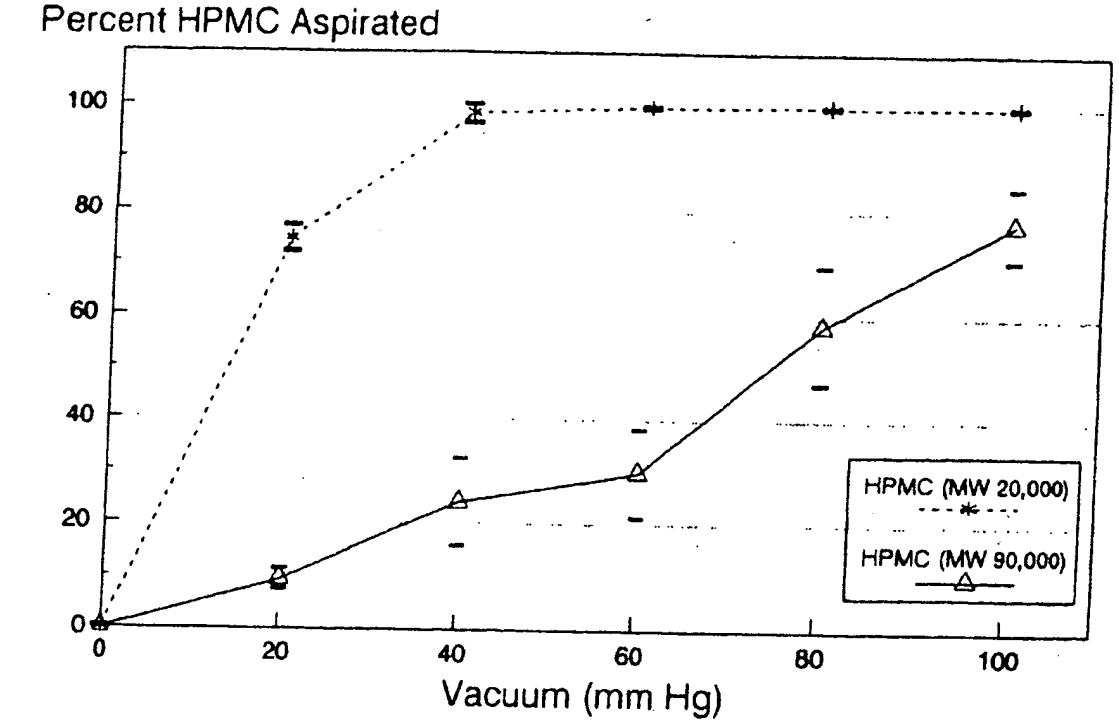
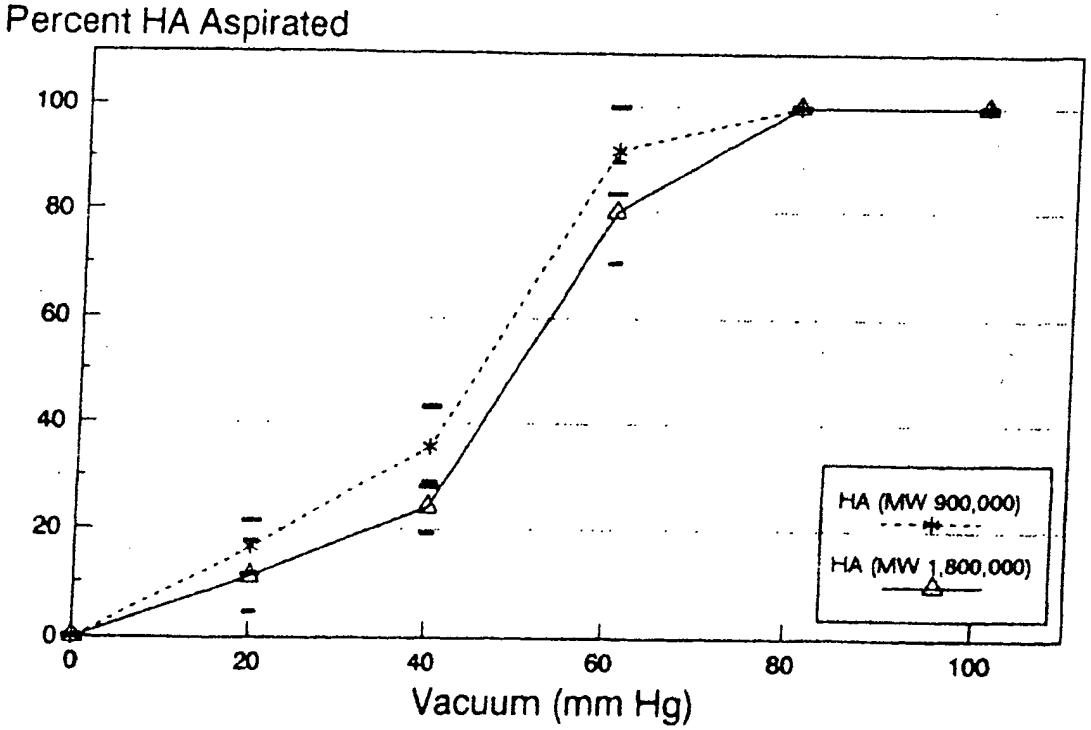


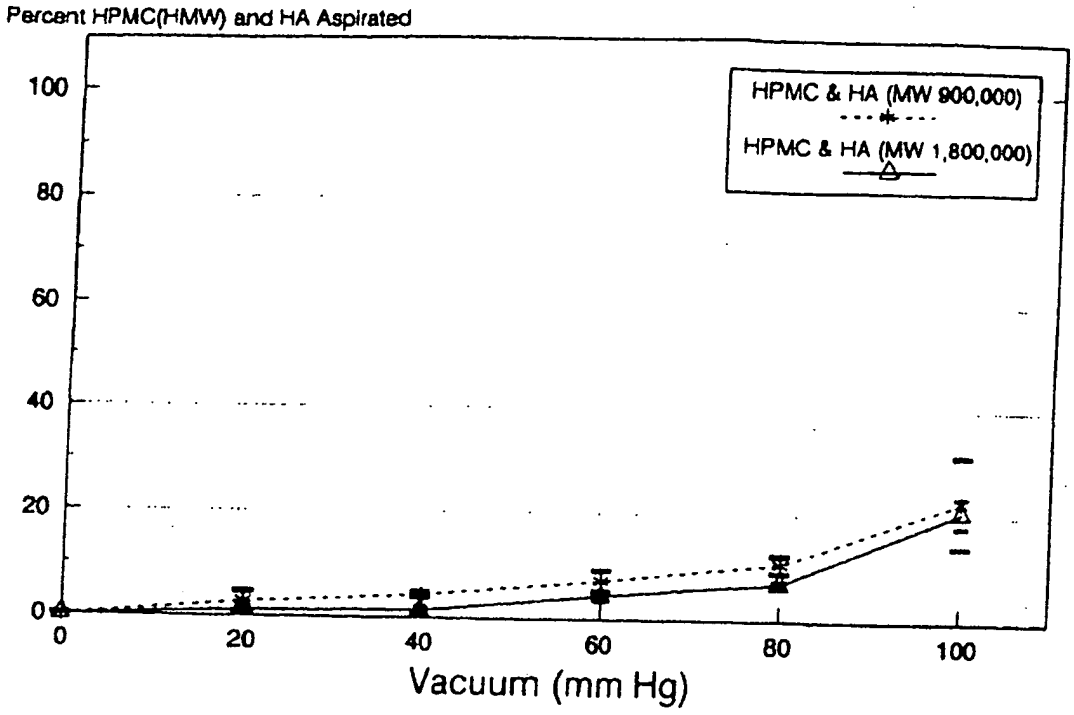
Figure 6. Viscosity at 0.35 s^{-1} for both high and low molecular weight HA and HPMC and mixtures of the two.

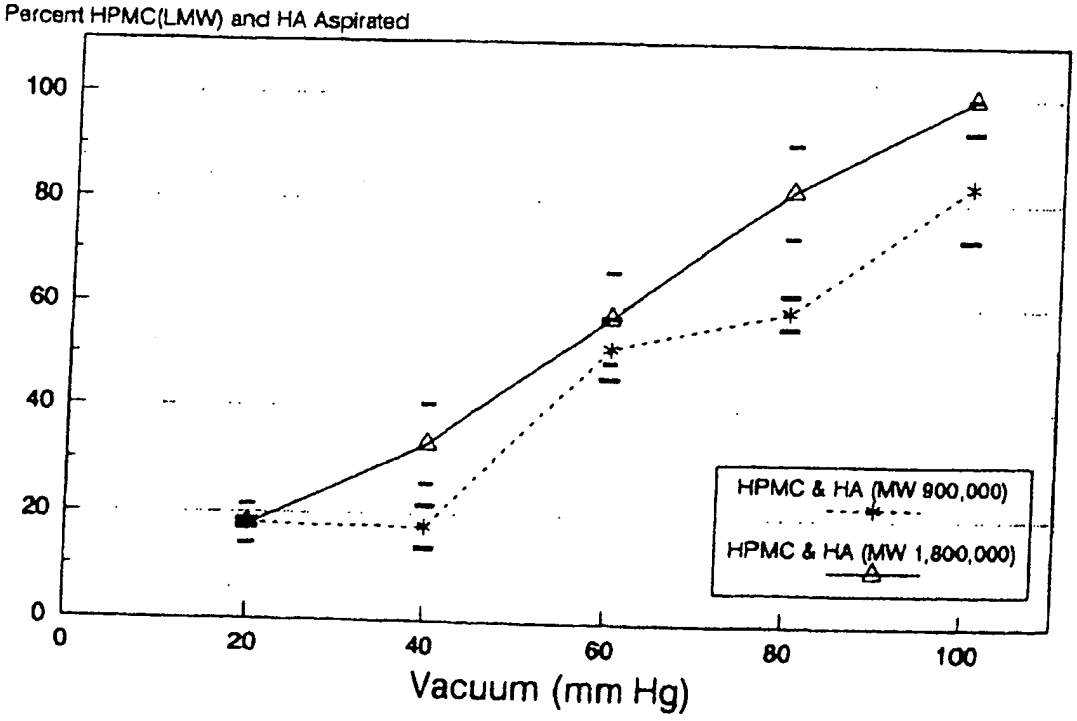
thetic polymers it is well known that the stiffness of a synthetic polymer increases with increasing molecular weight (see Aklonis and MacKnight[16] for example); however, the exact relationship between molecular weight and stiffness depends on the chain conformation and structure. Light scattering results indicate that the molecular weight of HA samples exceed 5 million with values of about 120 000 and 330 000 for the HPMC solutions. Clearly the difference in





Figures 7–10. Aspiration curves for HPMC and HA and mixtures. Data was obtained at increasing vacuums between 0 and 100 mm. Each sample was aspirated at fixed vacuum for 60 s and then the fraction removed was determined gravimetrically.





Figures 7–10. (continued).

solution behavior between HA and HPMC can in part be explained by differences in molecular weight.

The improved surface coating ability of HPMC as compared to HA is revealed by comparing the surface tension of these materials. Lower surface tension is observed with HPMC than with HA and appears to correlate with the formation of an endothelial coating by HPMC solutions. In general liquids spread when the surface tension of the liquid is lower than the critical surface tension of the surface.[17] Therefore, the critical surface tension of the corneal endothelium is likely to be between 43 and 62.7 dynes/cm, the values for HPMC and HA,

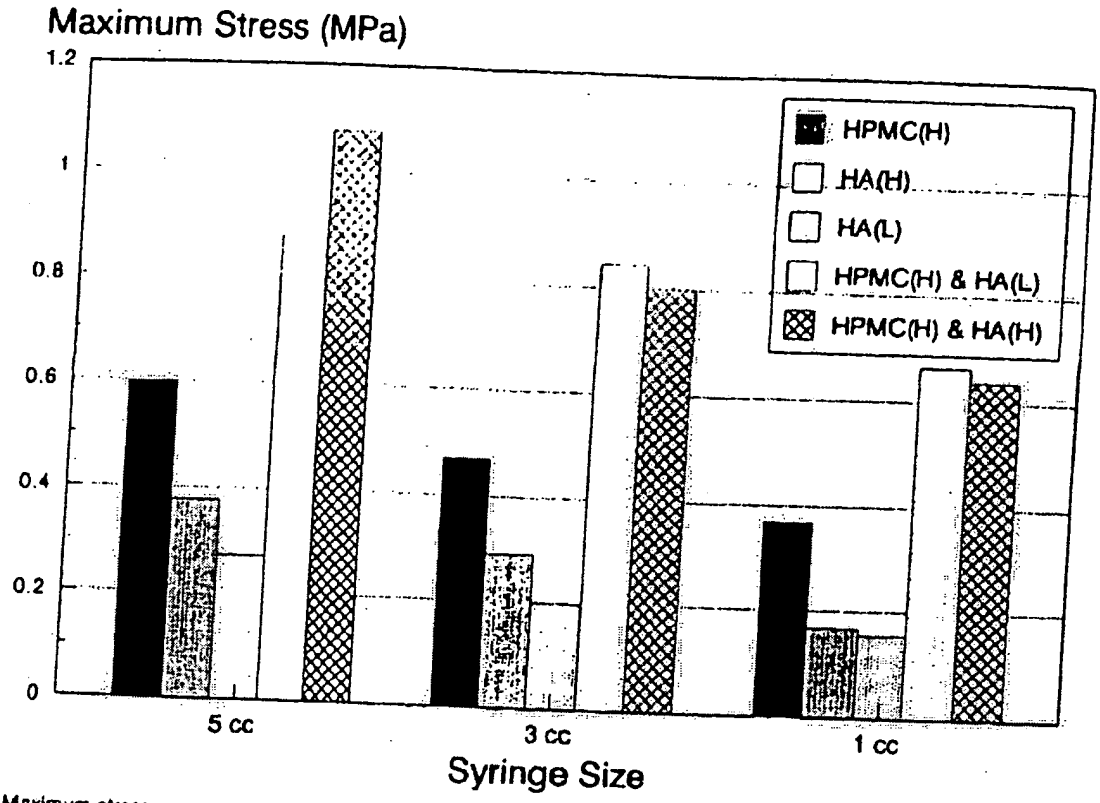


Figure 11. Maximum stress versus syringe size for high molecular weight HPMC [HPMC (H)], and low and high molecular weight HA [HA (L) and HA (H)], and mixtures of HPMC (H) with HA (L) and HA (H). Concentrations used of HPMC were 2%; those of HA were 1%. Mixtures contained 2% HPMC and 1% HA and therefore had higher stress values.

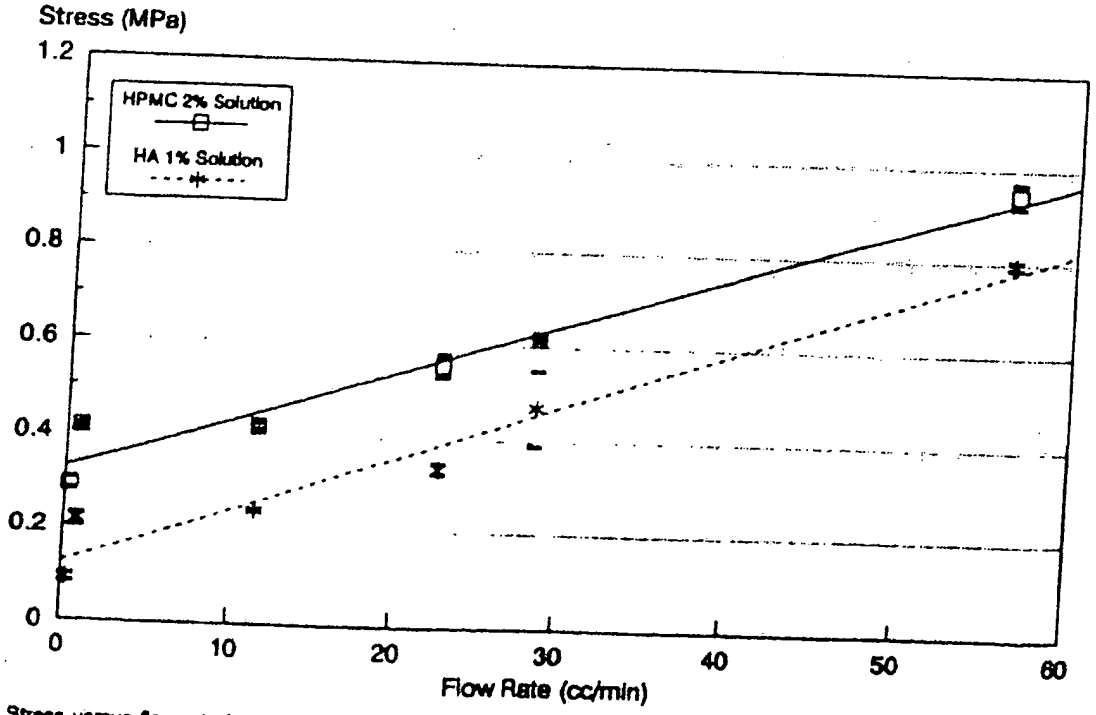


Figure 12. Stress versus flow rate for a 2% HPMC and 1% HA solution at strain rates of 200 and 500 mm/min. The strain rate (flow rate) was calculated as 22.6 and 56.6 mm/min for the 5-cc syringe, 11.40 and 28.50 mm/min for the 3-cc syringe, and 0.320 and 0.800 mm/min for the 1-cc syringe at strain rates of 200 and 500 mm/min, respectively.

respectively. Our results suggest that the addition of HPMC to HA solutions lowers the surface tension of the mixture and therefore is likely to provide an endothelial coating *in vivo*.

The aspiration behavior of HA and HPMC in the model system developed was quite different. Most of the HA aspirated as a "unit" between vacuums of 40 to 60 mmHg independent of molecular weight whereas HPMC solutions could be incrementally removed by small increases in vacuum. These results were consistent with clinical observations that HA aspirates as a "bolus" but HPMC can be removed incrementally.[1] Bolus aspiration of HA reflects to a first approximation the network forming ability of these high molecular weight molecules.

For some ophthalmic surgical procedures it is desirable that the solution remain in the eye during intraocular irrigation. If the solution aspirates easily, its space maintaining and tissue protective effects are diminished. On the other hand, some surgical procedures require complete and rapid removal of the polymer solution, because some patients are predisposed to forms of ocular trauma that promote the development of glaucoma.

The ability of a solution to maintain the deepness of the anterior chamber is also a function of its viscosity. At low shear rate, low viscosity fluids tend to flow more easily under the influence of gravity than fluids with high viscosity. In addition, the viscosity at high shear rates influences the aspiration and injection behavior of a viscoelastic. Although the low shear viscosity of HA (H) solutions was observed to be about six times that of even HPMC (H), HA solutions required only about half the stress to inject as HPMC. The stress required to inject these samples was, however, strongly dependent on the syringe diameter. All of the samples injected easily from 1-cc syringes. The high viscosity of HA solutions at low shear rates reflects a large axial ratio for the large HA molecules; however, at high shear rates the axial ratio must decrease thereby decreasing the viscosity.

An extension of this observation relates to the aspiration behavior of the samples. Although the HA samples aspirated as a unit over a small pressure range, the vacuum required to aspirate HPMC solutions was similar to that for HA solutions. These observations are consistent with the hypothesis that the high shear viscosity of HA solutions observed from the injection tests was not a significant factor in aspiration behavior under the conditions used in this study.

Solutions containing mixtures of HA (H or L) and HPMC (L) were observed to have the advantages of solutions containing either HA or HPMC. These mixtures had low surface tension, high weight average molecular weight and viscosity, and aspiration behavior that was similar to that of HPMC (L) along. This observation suggests that a viscoelastic with optimum surface coating and handling properties may be obtained by the use of a macromolecular solution containing a broad spectr of molecular weights and possessing a surface tension about 50 dynes/cm^2.

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GinShiCel MH

Hydroxy Propyl Methyl Cellulose

GinShiCel MH is a cellulose ether. Specifically Hydroxy Propyl Methyl Cellulose (a.k.a. Methyl Hydroxypropyl Cellulose, HPMC, MHPC) of off-white powders that are easily dispersed and dissolved in cold or hot water, to produce solutions of varying viscosities. Chemically, it is cellulose of short to very long chain length that has been etherified to a methyl hydroxypropyl ether to achieve an optimum balance of properties. GinShiCel MH is used as a viscosity and rheology modifier, protective colloid, water retention agent, stabilizer, and suspending agent, particularly in those applications where a nonionic material is desired.

Grades and Specifications

Different grades of Hydroxy Propyl Methyl Cellulose (HPMC) differ primarily in their solution viscosity, however, all grades can be enhanced with one or several modifications. These modifications add special performance characteristics of the product. These product modifications are available upon request, and are listed in Table 2. The following Table 1 details the available viscosities.

Table 1. Available Hydroxy Propyl Methyl Cellulose (HPMC) Viscosities.

GinShiCel MH Grade	Mean Viscosity*
GinShiCel MH C1	100
GinShiCel MH C4	400
GinShiCel MH 4	4000
GinShiCel MH 7	5500
GinShiCel MH 21	11000
GinShiCel MH 32	12500
GinShiCel MH 37	15000
GinShiCel MH 48	17500
GinShiCel MH 53	21000
GinShiCel MH 64	23000
GinShiCel MH 69	25000
GinShiCel MH 96	32000
GinShiCel MH 101	34000
GinShiCel MH 117	38000
GinShiCel MH 128	39000
GinShiCel MH 133	40000
GinShiCel MH 144	45000
GinShiCel MH 256	48500
GinShiCel MH 336	60000
GinShiCel MH 512	9000**
GinShiCel MH 592	10000**

*Brookfield RVT, 2%, 20°C
**Brookfield RVT, 1%, 20°C

Table 2. Available Modifications

Suffix	Product Modification	Explanation
S	Surface Treated	Ensures cold water dispersion
A	Sag Resistent	Provides sag resistent property
L	Slip Resistent	Provides slip resistent property
X	Extended Open Time	Extends the open time of mortar

Physical Properties:

Appearance	White to off-white
Particle size	99% < 250μm
Moisture	Max 5%
Ash Content	Max 1%
Salt Content	Max 3%

Applications

Construction Industry

Hydroxy Propyl Methyl Cellulose (HPMC) improves bonding plaster and machine plaster masses based on plaster or lime gypsum and in hydraulically bonding masses such as finishing mortar, fillers, tile adhesives and PM binders based on cement with water-retaining properties for adhesion and workability.

Hydroxy Propyl Methyl Cellulose (HPMC) act as plasticizers, bonding additives, floating agents, and in finishing coats based on synthetic resin as a stabilizing and thickening agent.

Coatings Industry

With Hydroxy Propyl Methyl Cellulose (HPMC) products the rheology and consistency can be adjusted in lacquers and paints, and pigments and fillers are stabilized.

Suspension polymerization

Low viscosity types of Hydroxy Propyl Methyl Cellulose (HPMC) are used as protective colloids in the production of S-PVC. They affect particle size distribution, porosity, plasticizer absorption and bulk density of the PVC.

Ceramics
Hydroxy Propyl Methyl Cellulose (HPMC) are used as plasticizers and green strength agents in modern, non-plastic compositions for high-tech ceramics. Non-plastic ceramic masses are transformed into an extrudable plastic mass by adding GinShiCel MH and water, under the influence of shear forces.

Tobacco Industry
Hydroxy Propyl Methyl Cellulose (HPMC) Food Grade cellulose ethers are used as binders and film formers in the manufacture of reconstituted tobacco sheets and flakes, and as adhesives for cigarette paper and cigar seams.

Detergents and cleaners

Low viscosity Hydroxy Propyl Methyl Cellulose (HPMC) types increase the ability of laundry detergents to suspend dirt particles and color fastness in fabrics and inhibit graying.

Pharmaceutics Industry

Hydroxy Propyl Methyl Cellulose (HPMC) Pharm Grade is also used in the production of medical plaster bandages.

Cosmetics Industry

Due to their thickening and stabilizing effect and their good skin compatibility, Hydroxy Propyl Methyl Cellulose (HPMC) Pharm Grade are suitable for use in emulsions, toothpastes, shampoos, soaps, creams, ointments and lotions.